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The Nature of Dynamic Arteriolar Vasoreactivity: A Mini-Review and A Classification Scheme

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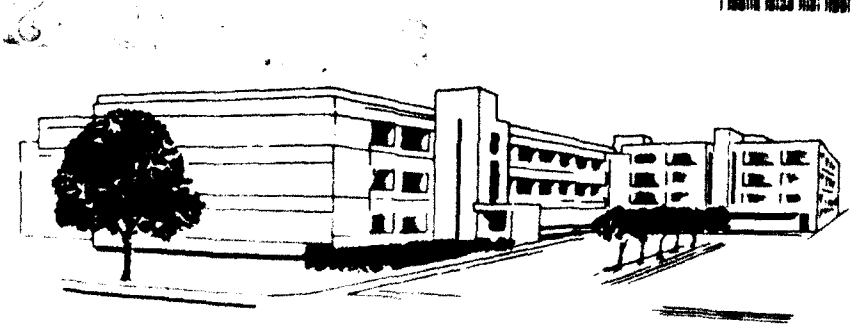

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Changes in microvascular caliber are frequently observed both during normal, resting physiological conditions, as well as during physiologic stresses such as hemorrhage and fluid volume resuscitation. Many of the dynamic changes have been described with the singular term vasomotion. However, many types of frequently observed vasomotive behavior are atypical of either microvascular inactivity or vasomotion. This review describes a simple classification scheme for four types of arteriolar behavior observed routinely in our laboratory in the microvasculature of skeletal muscle of the anesthetized rabbit. These patterns include inactivity (static diameter of the open vessel which does not dynamically affect flow), vasoactivity (random, non-rhythmic changes in vessel diameter, which effect step-wise or non-rhythmic increases or decreases in flow), vasomotion (regular, rhythmic, repetitive constriction and dilation of arterioles with either a fast or slow period) and vessel closure (closure occludes flow entirely, and may divert flow to other adjoining microvascular beds). Although these patterns may not represent a functional continuum, each pattern of behavior is distinct in its effect on blood flow. Therefore, our study proposes a simple classification scheme, which will aid in understanding the dynamic response of the microvasculature to moderate or severe physiologic stress as well as the local, dynamic regulation of microcirculatory flow during pathophysiologic states.

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Changes in microvascular caliber are frequently observed both during normal, resting physiological conditions, as well as during physiologic stresses such as hemorrhage and fluid volume resuscitation. Many of the dynamic changes have been described with the singular term vasomotion. However, many types of frequently observed vasomotive behavior are atypical of either microvascular inactivity or vasomotion. This review describes a simple classification scheme for four types of arteriolar behavior observed routinely in our laboratory in the microvasculature of skeletal muscle of the anesthetized rabbit. These patterns include inactivity (static diameter of the open vessel which does not dynamically affect flow), vasoactivity (random, non-rhythmic changes in vessel diameter, which effect step-wise or non-rhythmic increases or decreases in flow), vasomotion (regular, rhythmic, repetitive constriction and dilation of arterioles with either a fast or slow period) and vessel closure (closure occludes flow entirely, and may divert flow to other adjoining microvascular beds). Although these patterns may not represent a functional continuum, each pattern of behavior is distinct in its effect on blood flow. Therefore, our study proposes a simple classification scheme, which will aid in understanding the dynamic response of the microvasculature to moderate or severe physiologic stress as well as the local, dynamic regulation of microcirculatory flow during pathophysiologic states.

THE NATURE OF DYNAMIC ARTERIOLAR VASOREACTIVITY: A MINI-REVIEW AND A CLASSIFICATION SCHEME

Stephen P. Bruttig, Per Borgström, J. André Schmidt, Karl -E. Arfors and Marcos Intaglietta

INTRODUCTION

Thanks to intravital microscopy and on-line data acquisition, dynamic, microvascular phenomena are subjects of increasing interest. A dynamic flow regulating process (vasoreactivity) which is currently receiving much attention is the phenomenon of vasomotion. However, the phenomenon, even the name, is rooted in another generation (1). Older still is a reference to the same phenomenon which was referred to as "peristalsis 'of small blood vessels'" (described by Robert Whytt in Physiological Essays in 1750 and cited by Mayerson, 2). Vasomotion is most frequently described as the rhythmic opening and closure of arterioles (3-12), although there are references to this activity in venules (4,13) and even capillaries (14).

Currently, vasomotion in skeletal muscle is considered to be a rhythmic process which operates at one of two periods -- i.e., "fast wave" = 3-6 seconds and "slow wave" = 25-35 seconds (9,12,15-17). In addition, vasomotion is thought by some to be regulated in some fashion by higher nervous control (7-9,18,19 as cited in 4). Finally, vasomotion is thought to be coupled between terminal and pre-terminal arterioles (7-9).

Although these characteristics of vasomotion have been well described, a clear, common definition of vasomotion has not emerged from the scientific literature. Nicoll and Webb (20), pioneers in the study of vasomotion, avoided the question of rhythmicity, and concentrated instead on fast and slow ("peristalsis") vasomotion, and on the types of control (central nervous; local demand; physical factors such as temperature). Faber et al. (21,22) described vasomotion as "enhanced rhythmic contractile activity...for arterioles". Their typical tracings showed only synchronous activity (21). Salerud et al. (23) studied the "rhythmical variations in microcirculatory blood flow" in their experiments on

vasomotion; apparently excluding (as a separate dynamic flow regulatory category) arrhythmic or asynchronous variations in blood flow. Colantuoni et al. (24) described vasomotion as the "spontaneous time-dependent contraction and relaxation of small arteries, arterioles and in some instances venules". However, their figures indicated that they accepted as vasomotion both synchronous and asynchronous microvascular reactivity (6,24). A similar approach was taken by Slaaf et al. (16) and Vrielink et al. (15). They described vasomotion as "rhythmic changes in vascular diameter" (15), but they presented data indicating that they accepted both synchronous and asynchronous arteriolar reactivity. Meyer et al. (9) and Bouskela (25) returned to the original concept of rhythmicity (implying synchronous arteriolar behavior) as they studied vasomotion. Riva et al. (26), defined vasomotion as "spontaneous rhythmic activity of the small vessels". Finally, Yip et al. (27) indicated that "arterioles and sometimes venules ... possess spontaneous quasiperiodic rhythmic contractile movement (vasomotion)". Thus, consensus would indicate that vasomotion is a rhythmic, time-dependent, repetitive contraction and relaxation of arterioles (and venules in some preparations), which serves to dynamically regulate perfusion of the capillary beds. Therefore, in this study, we will define vasomotion as regular, rhythmic and repetitive arteriolar constriction and dilation.

Although much recent attention to microvascular reactivity has focussed on periods of inactivity and periods of vasomotion, other types of microvascular behavior are evident which cannot be considered either vasomotion or inactivity. In addition to vasomotion, we have observed a second type of intermittent constriction and dilation, but its occurrence is considerably more random and non-uniform than vasomotion. This type of vasoreactivity has heretofore been included in the term vasomotion by those authors who accept asynchronous vasoreactive behavior as typical of vasomotion. We also observe microvascular closure as a clearly distinguishable option to control blood flow.

A few authors refer to certain vasoreactive processes as flowmotion. For the sake of clarity, flowmotion, which has been described in some experiments as well (3,12), refers to the downstream (distal) changes in blood flow regulated by changes in vascular caliber at upstream (more proximal) arteriolar sites. Flowmotion can be observed by intravital microscopy or by laser doppler flowmetry (LDF). In our hands, flowmotion, as represented by LDF, displays the same periodic characteristics as those described for vasomotion (10,28). Therefore, in the present studies, we will consider LDF patterns to represent overall microvascular flowmotion (vasomotion) within a subscribed tissue segment. Furthermore, we will use these flowmotion patterns as examples of the distinctions between various types of dynamic arteriolar activities (i.e., inactivity, vasoactivity and vasomotion; closure cannot be readily identified by LDF unless an entire microvascular bed closes; in our hands, venular microvessels were quiescent).

To understand the role that such vasoreactive processes play in the delivery of blood at the tissue level, one must be able to adequately classify the vasoreactive behaviors and then evaluate the parameters describing each process (i.e., rate, occurrence, onset, disappearance, amplitude, coupling, etc.). The task might be facilitated by a systematic analysis of the components of vasoreactivity, which is not complicated by the problems of quantifying rapid, rhythmic events co-mingled with random, arrhythmic behavior. This report describes a simple approach to characterizing and categorizing vasoreactive phenomena from two independent measurements of microvascular blood flow dynamics; namely, laser Doppler flowmetry (LDF) and intravital microscopy. Due to general correlation between videotape records and coincident LDF records, the LDF records will be used to emphasize differences within the classification scheme.

METHODS

Animal Model. The data analyzed in this study came from previous experiments studying the systemic and microvascular responses to controlled hemorrhage (10,11). Briefly, New Zealand White rabbits (1.00 +/- 0.15 kg) were sedated with Hypnorm, anesthetized with urethane and prepared for intravital microscopic study of the tenuissimus (skeletal) muscle as described previously (10,11,29).

Vascular Architecture. The rabbit tenuissimus muscle preparation is characterized by a central supply artery which courses longitudinally through the muscle. Transverse arterioles leave the supply artery at intervals. These transverse arterioles cross the muscle perpendicular to the longitudinally-oriented muscle fibers. The transverse arterioles in turn give off terminal arterioles into the long axis of the muscle fibers. The terminal arterioles eventually arborize into a capillary network within the muscle fiber bundle itself. From our experience, flow into each terminal arteriole is regulated by a sphincter-like structure near the origin of the microvessel from the transverse arteriole (10). Approximately seventy percent of the transverse arterioles continue across the muscle fiber bundle and enter the surrounding connective tissue into which they, too, arborize into capillary networks (30). Vascular drainage from either the muscle fiber bundle or the surrounding connective tissue is effected by networks of venules and small veins. In this videomicroscopy study we always examined a junction of a true transverse (TR) and a true terminal (TE) arteriole within the muscle fiber bundle (Fig. 1).

Instrumentation. The microvessels of the tenuissimus muscle were viewed through a Leitz intravital microscope described previously (10), using a 50x objective (numerical aperture = 1.0). Microscopic observations were continuously recorded using a super VHS videotape recorder (RCA, Model No. VPT695HF, Indianapolis, IN). Microvascular vasoreactive patterns were evaluated off line from analysis of those videotapes. Microvascular flow patterns were also

observed and recorded using a laser doppler flow probe (TSI Laserflo, model BPM 403A, 0.8 mm probe; TSI Incorporated, Medical Instruments Group, St. Paul, MN), placed with the aid of the microscope, onto neighboring sites on the tenuissimus muscle or the gastrocnemius muscle. Arteriolar behavior was assessed by comparing the activity appearing on the videotape with that observed by LDF (9). Since the correlation was quite good (9), we will present selected LDF records to emphasize the distinct characteristics of the various types of arteriolar behavior.

In order to distinguish types of vasoreactivity particular to either transverse or terminal arterioles (a process which cannot be accomplished by LDF), comparisons of vascular wall behavior were made from intravital videomicroscopy records. Vasoreactive behavior of the microvessels was evaluated from the videotape records for 20 second periods and scored (i.e., inactivity = 0, vasoactivity = 0.5, vasomotion = 1.0, closure = 1.25). Data from the above evaluation (the 20 second scores) were then plotted on a time line for each vessel type (excerpts of these data for transverse or terminal arterioles are shown in Fig. 2). Initial comparisons consisted of qualitative inspections of the behavior patterns between vessel types along the length of the time line.

RESULTS

Vascular Wall Activity. The animals in these experiments were studied during a 10 minute control period and for 30 minutes following a fixed-volume (30%) hemorrhage from the carotid artery (10). Continuous flow with no discernable vascular wall activity was identified as inactivity (Fig. 3). The regular, rhythmic and repetitive contraction and relaxation of the microvascular wall with a period of 25-35 seconds and a frequency of 1-3 cycles per minute was identified as slow wave vasomotion (Fig. 4). Slow wave vasomotion was not always evident in the frame-by-frame videotape analysis, but was easily detected from the LDF records. A second type of vasomotion (fast wave) was characterized by a period of 3-6 seconds and a frequency of 10-20 cycles per minute. Fast wave vasomotion in transverse arterioles effects rhythmic constrictions to approximately 50% of the vessel diameter, while fast wave vasomotion in the terminal arterioles represents complete, momentary closure of the microvascular orifice (sphincter). Fast wave vasomotion was also easily detected by LDF, due to synchrony of red cell flux in any terminal arteriole and the capillaries and venules which arborize from it within the tissue segment monitored by the LDF probe. Examples of both types of vasomotion, identified by LDF tracings, are presented in Fig. 5. Although fast wave vasomotion could be observed in both the terminal and the transverse arterioles (by intravital microscopy), slow wave vasomotion appeared to be restricted to the transverse (pre-terminal) microvessels.

A second type of microvascular reactivity, clearly distinct from the regular patterns presented as vasomotion, was identified by its random, arrhythmic vascular wall activity with no discernable regular period. We identified this arrhythmic, dynamic activity as vasoactivity (Fig. 6). We distinguished this activity from vasomotion by its non-rhythmic, asynchronous, and randomly occurring nature. Finally, when arterioles remained completely closed for periods in excess of 15 seconds, we identified the microvascular behavior as closure. Closure represented the complete approximation of the microvascular walls,

primarily in the vicinity of the sphincter, occluding flow for periods in excess of a few seconds (usually many seconds to a few minutes). As a local microvascular phenomenon, closure could not be distinguished by LDF. When closure was observed (e.g., with intravital microscopy), it was often seen at very low arterial pressures (20-30 mmHg), such as those resulting from rapid, severe hemorrhages.

Typical results from this type of qualitative analysis are shown for 5 of the anesthetized rabbits subjected to a 30% fixed- volume hemorrhage (Fig. 2). Most arterioles showed very little or no vascular wall motion (i.e., were inactive) during the control period. However, with the onset of the hemorrhage, most arterioles exhibited increasing amounts of some type of vasoreactivity (vasoactivity, vasomotion, or closure). Sometimes these activities were short-lived and other times they persisted throughout the spontaneous recovery period.

A consistent finding was an apparent lack of coupling of vascular wall activity (vasoactivity or vasomotion) between transverse (pre-terminal) and terminal arterioles in these rabbits; apparent because during periods of reactivity in the terminal arteriole, there was no correlative reactivity in the parent transverse arteriole (Fig. 2). However, when terminal arterioles were quiescent, transverse arterioles were quiescent at the same time. The question of coupling between terminal and transverse arterioles remains unresolved. Finally, there was no consistent pattern for interbehavior correlation (i.e., vasomotion was not always preceded or succeeded by vasoactivity).

Similar information can be obtained from the laser doppler flowmetry records (i.e., inactivity, vasoactivity and fast or slow wave vasomotion). Several examples of each type of activity pattern have been presented to provide the reader some familiarity with the pattern recognition. Figure 3 shows examples of microvascular inactivity as determined by LDF. Figures 4 and 5 show several examples of vasomotion, and both fast and slow wave vasomotion are represented. Note the regular, rhythmic and repetitive nature of the

microvascular flow pattern, which persisted for varying, but extended periods of time. Figure 6 shows several examples of vasoactivity. Although there were definite alterations in microvascular flow activity during periods of vasoactivity, there was no consistently recognizable regularity or period. Comparison of these records (i.e., Figs. 3,4,5,6) clearly indicates that a pattern of microvascular flow activity which was neither inactivity nor vasomotion, but which must be considered in describing and understanding microvascular flow dynamics. Furthermore, these records indicated the variability of the various types of flow activity.

DISCUSSION

Vasoreactive phenomena are recruited physiologically in response to a variety of stresses, and it is not surprising that one of those vasoreactive phenomena is arteriolar vasomotion. However, the available scientific literature describing vasomotion certainly falls short of consistency, in definition, choice of animal model and/or discussion of its effect on physiologic regulation. As a result, the definition of vasomotion varies among authors (3; see also INTRODUCTION). Furthermore, the sophistication of both data collection and the quantitative measures to characterize or assess vasomotion varies significantly among laboratories. Thus, a common understanding of the physiologic role of vasomotion in the local regulation of tissue perfusion is yet to be advanced, let alone endorsed by the general scientific community. Moreover, a wide range of experimental animals, both conscious and anesthetized, have been studied in the attempt to understand the phenomenon of vasomotion. These animals (to include man) have been studied either as conscious or anesthetized subjects. The fact that such a variety of experimental animals (spanning genera, species and sex) may respond differently to similar physiologi- perturbations, or respond in a similar fashion, but by fundamentally different mechanisms, makes the formulation of a single unifying hypothesis regarding vasomotion improbable. Consequently, a simple scheme for categorizing the variety of phenomenologic observations collectively known as vasoreactivity may offer a way to organize the ever-increasing information base of dynamic, vasoreactive processes.

The method of analysis used in our study describes and characterizes the dynamic reactivity of various microvascular components during responses to many types of hypoperfusion, including hemorrhagic hypotension. Certainly, this analytical method may be applied to the microvascular responses to other physiologic perturbations as well.

We have been able to demonstrate conclusively that dynamic vasoreactive responses in the terminal

arteriole are not necessarily linked (coupled) to those in the pre-terminal arteriole (compare the qualitative time line for transverse arterioles with that for terminal arterioles; Fig. 6). This is consistent with earlier observations and comments by Baez (5).

These results indicate several features regarding the nature of vascular reactivity. First, a difference between pre-terminal and terminal arterioles in skeletal muscle is distinguishable. Thus, when vasomotion occurs in terminal arterioles, the microvessels open and close completely, whereas in the transverse arterioles, the vessels constrict to only 50% of their original diameter (at most). Second, neither vasoactivity nor vasomotion in a terminal arteriole necessarily coincides with vasomotion in a transverse arteriole. Third, when circumstances allow direct visualization of two adjacent terminal arterioles in the same microscopic field, observation of vasomotion in one terminal arteriole does not necessarily guarantee observation of vasomotion in the other terminal arteriole. Similarly, although both arterioles might exhibit vasomotion, they might be out of phase with eacn other. This lack of coordination supports the notion of individual pacemakers which regulate vasomotive frequency (9). Furthermore, vasomotion was observed more often in the terminal than the pre-terminal (transverse) arteriole. Therefore, it is reasonable to assume that any pacemaker may, in fact, be located in the terminal arteriolar structure.

Pacemaker activity itself differed between the terminal and the transverse (pre-terminal) arteriole. When vasoactivity or vasomotion was observed in the transverse arteriole, it occurred along the entire length, with somewhat diminished reactivity at the distal end (near the connective tissue). Vascular reactivity in the terminal arteriole was confined to the sphincter-like structure at the origin of the terminal arteriole, with no change in the diameter of the terminal arteriole distal to the sphincter.

The contrast of reactivity along the entire length of the transverse arteriole, with only local reactivity in the terminal arteriole, might lead one to suspect

propagation of reactivity along the transverse arteriole to "receptive" terminal arterioles. However, the absence of vasoreactivity in transverse arterioles during periods of sustained reactivity in the terminal arterioles argues against that idea. A more likely notion is that individual terminal arterioles respond locally, as needed, and when summation from the pacemakers of individual terminal arterioles is sufficiently large, reactivity in the transverse arteriole is recruited as well. Thus, one could explain "coupled vasomotion" (i.e., coincident vasomotive behavior in both the pre-terminal and terminal arterioles) on the basis of both anti-dromic and orthodromic conduction of the pacemaker signal. When vasomotion is not coupled between the two vessel types (i.e., dysjunction), it may indicate that the anti-dromic signal is too weak or is being overridden by other local or central controls. Such a possibility is consistent with hypotheses advanced by Colantuoni et al. (6).

Vasomotor control may also be exerted via modulation of either adrenergic or neuropeptide-secreting neural activity (31). The anatomic and pharmacologic basis for this possibility has been described in part by Ohlen et al. (32,33) but not with specific reference to vasomotion. In addition, the physiologic basis for endothelial modulation of vasomotion has been partially investigated by Bouskela et al. (34) who have shown that vasomotion is not affected by interference with EDRF-NO. Furthermore, local metabolites or endothelial cell signal modulation may override any neural control of vasoreactivity (35). Moreover, it is likely that certain physiologic, pharmacologic, or patho-physiologic conditions serve to couple or uncouple the vasomotive behavior in these vessels, leading to the disparate results among the various authors. However, until these phenomena (i.e., vasoactivity, vasomotion, and closure) are investigated more vigorously and more consistently, phenomenological contradictions may continue, even though the same preparations are used in the same laboratories.

Although the results of our study concerning the coupling of vasomotive activity between succeeding

vascular segments are similar to earlier findings (12,28,36), they contradict (partially or completely) recent findings by other investigators using the same animal preparation (6-9,15,16,34). The differences in findings (i.e., coupling of vasomotion in pre-terminal and terminal arterioles) could be a function of the method of analysis of the data, and a more rigorous comparison of the analytic methods may reveal the discrepancies. However, an argument for the complete validity of these observations, including the rarity of vasomotion in the control period as well as the initiation of vasomotion following hemorrhage, rests in the similarity of our results with those of Gustafsson et al. (37). In that study, they conducted similar experiments with two different types of instrumentation to monitor microvascular blood flow, and the experiments were conducted in rat rather than rabbit. Thus, neither the method of analysis nor the species of experimental animal appears to be critical for obtaining results such as those reported in the present study.

Finally, physiologic significance is always questioned in regard to a weakly understood phenomenon such as vasomotion. Intaglietta (12) provided a physiologic role for vasomotion in controlling local tissue perfusion pressure, fluid reabsorption from tissue under conditions of hypoperfusion, and red cell flux at average arteriolar diameters which would normally restrict red cell passage. The latter role is discussed more completely by Borgstrom et al. (10). In addition, Baez (5) discusses vasomotion as distinct from "autoregulatory reactions", but as having a direct effect on delivered blood volume, spacing between capillaries, capillary hematocrit, capillary hydrostatic pressure, and fluid exchange. The emerging literature on vasomotion (most likely vasoactivity and closure as well) reveals a basic cardiovascular (microvascular) effector mechanism which appears to be employed by different animals in response to various and different stimuli. Although some investigators observed vasomotion with regularity under control conditions (6-9,15,16,34), others did not (10,11,28). Studies such as ours have stressed that these vasoreactive phenomena are recruited, as needed, in

response to pathophysiologic deviations from control conditions.

Fundamental to understanding vasomotion, vasoactivity, or closure is the concept that these are legitimate physiologic effectors which are recruited oftentimes to restore normal physiologic function, a conclusion reached by others in this field as well (12,28). The fact that these phenomena may or may not occur during control conditions should raise questions not so much about the normalcy of the preparation as about our understanding of these microvascular effector mechanisms. Therefore, we believe that consideration of all four patterns (i.e., inactivity, vasoactivity, vasomotion, and closure) allows distinctions to be made among the responses of different types of arteriole in a specific sense and among markedly different physiologic conditions in a general sense.

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Figure 1. A photograph of an arteriolar junction from the videotape record of typical experiment. The larger vessel is the transverse (pre-terminal) arteriole; the smaller vessel is the terminal arteriole. Note the muscular sphincter-like structure at the origin of the terminal arteriole. Regardless of most downstream dilation, the internal diameter through this sphincter determines capillary perfusion within the muscle fibers. **Panel A** shows the arteriolar junction with an open (i.e., unconstricted) sphincter. **Panel B** shows the arteriolar junction with a closed sphincter. The wide vertical columns in this photo are individual muscle fibers.

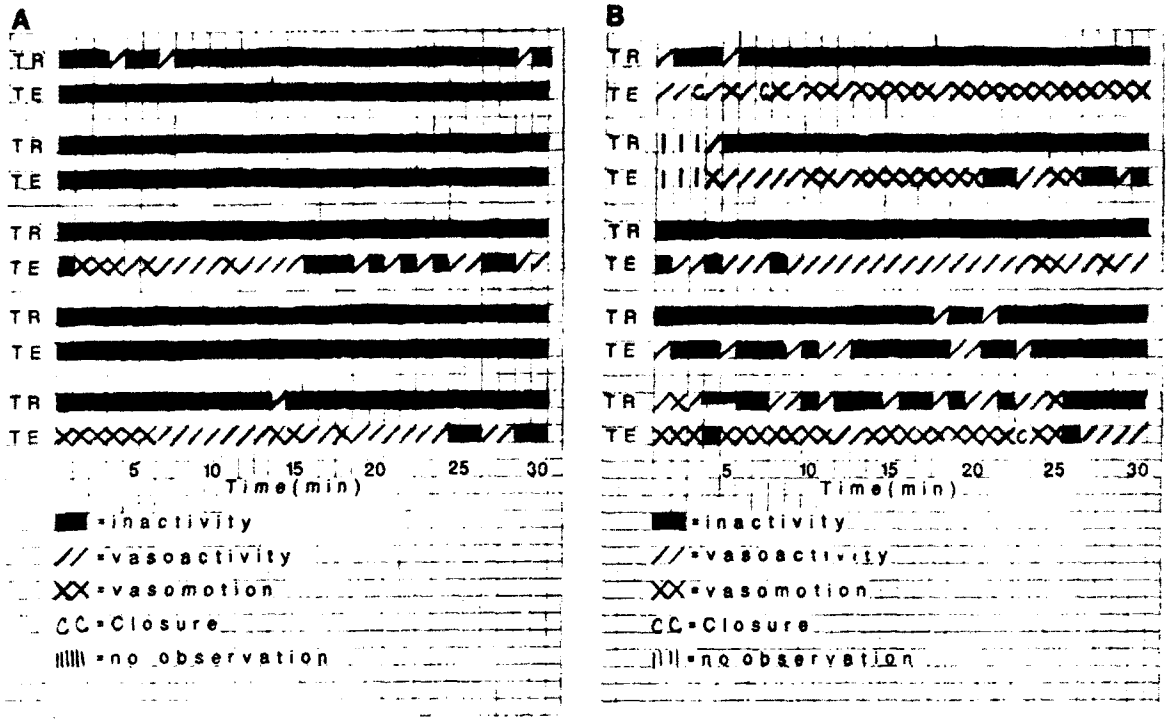

Figure 2. Excerpts of actual raw data scores for microvascular activity in terminal (TE) and transverse (TR) arterioles of 5 rabbits. Each box represents 20 seconds. Figure 6A shows the microvascular behavior during the control (pre-hemorrhage) period. Note that most vessels, display very little or no vasomotion. Figure 6B shows the microvascular behavior during part of the post-hemorrhage (spontaneous recovery) period. Note the presence of increased microvascular activity, but with little correlation between the transverse and the terminal arterio.e.

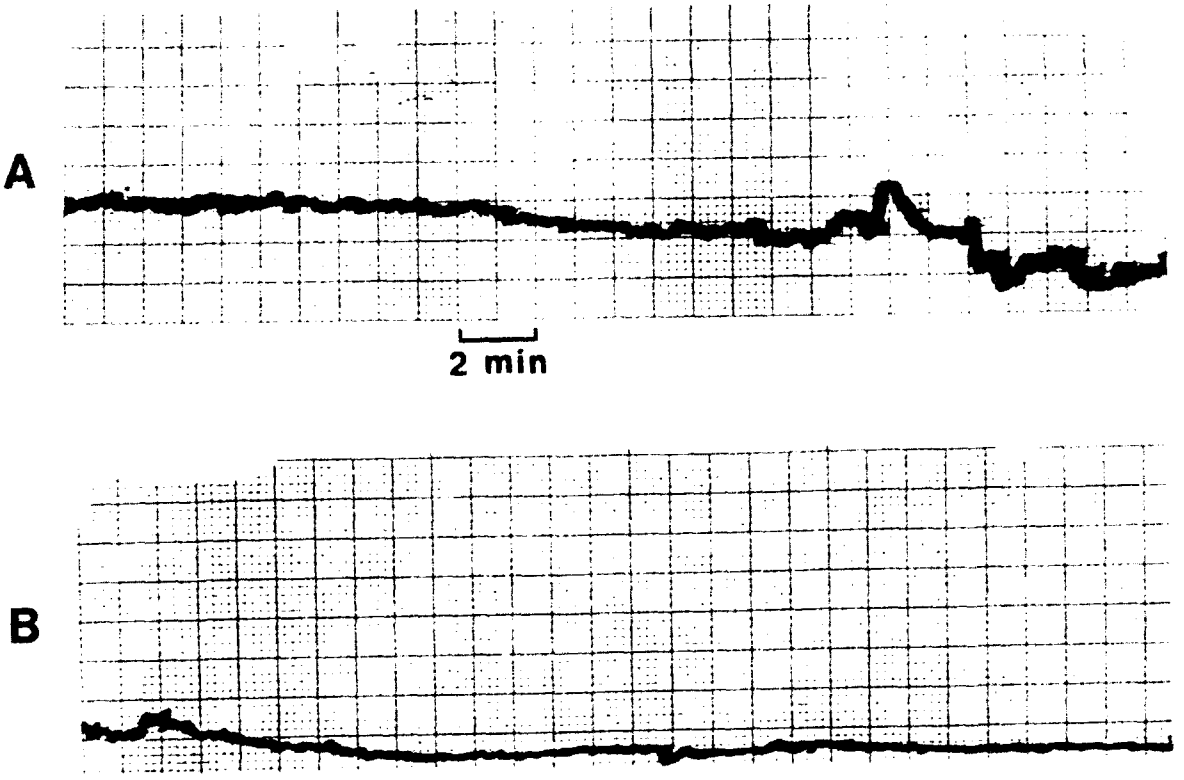

Figure 3. Microvascular inactivity, demonstrated by representative laser Doppler tracings of blood flow in skeletal muscle (tenuissimus or gastrocnemius). The probe diameter was 0.8 mm. Although there are occasional changes in blood flow, there are no continuous synchronous or asynchronous flow patterns.

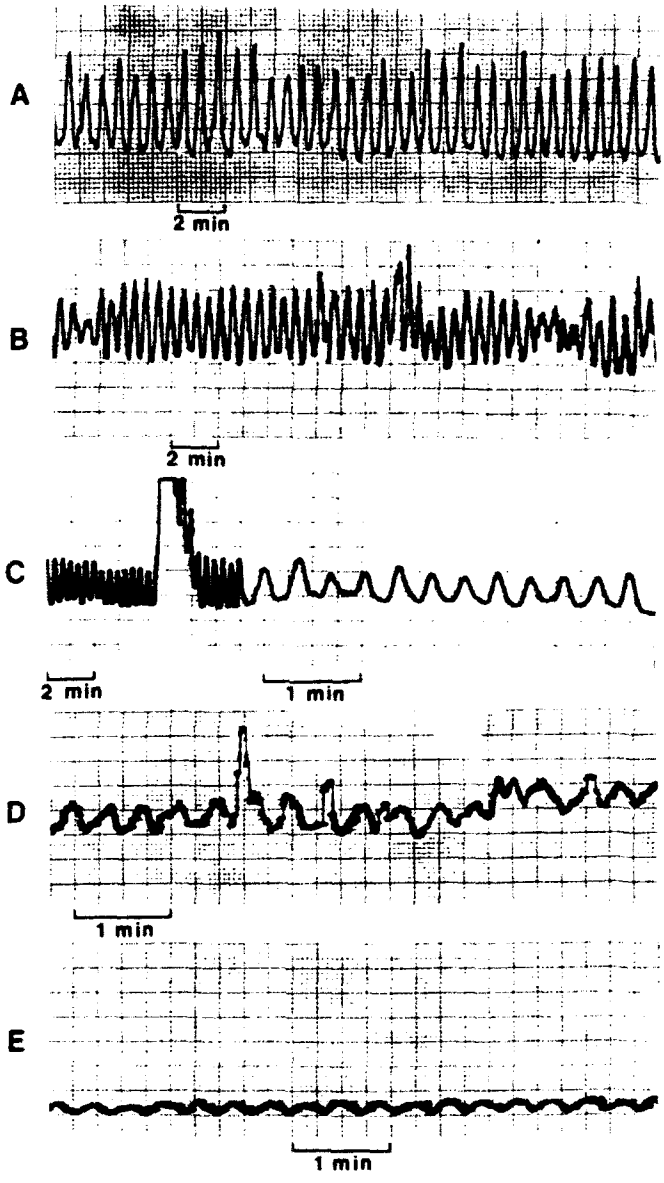

Figure 4. Microvascular vasomotion, demonstrated by a series of representative laser Doppler tracings of skeletal muscle blood flow. Note that all tracings demonstrate regularity, rhythmicity, and repetitiveness. In some tracings, chart speed has been increased for emphasis. All tracings demonstrate "slow wave" vasomotion.

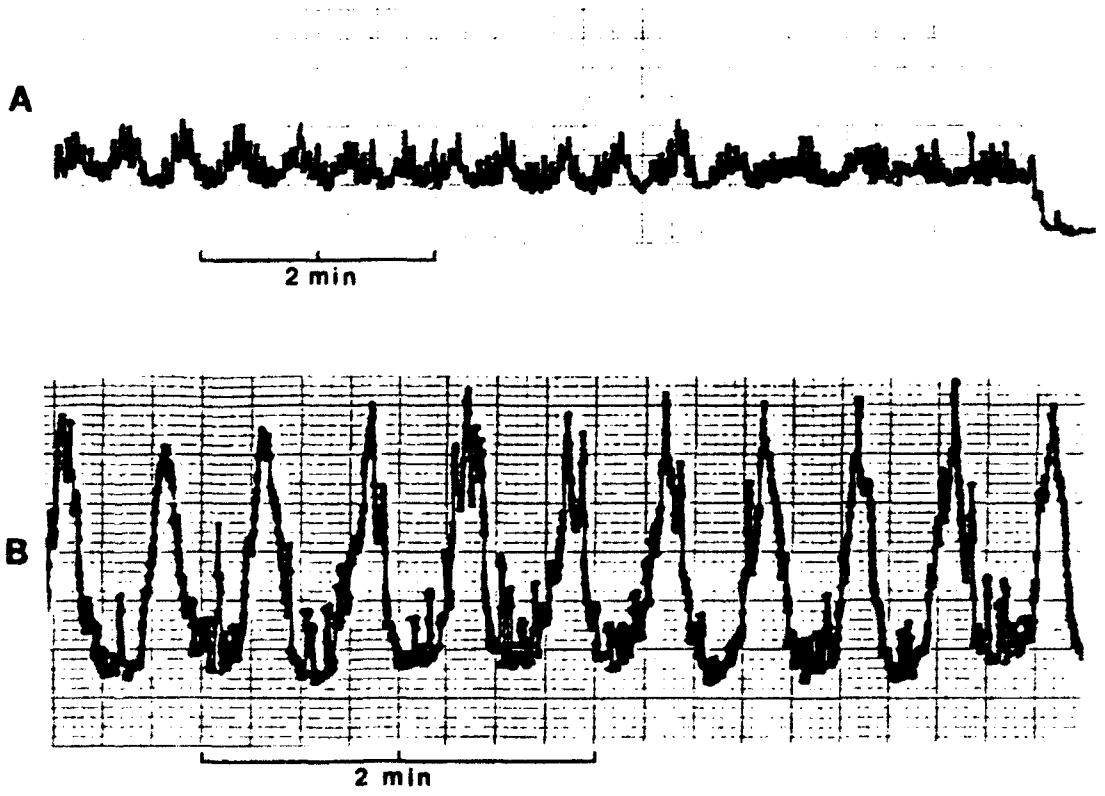

Figure 5. Microvascular vasomotion, demonstrated by representative laser Doppler tracings of skeletal muscle blood flow. Both panels show "slow wave" vasomotion, overridden by "fast wave" vasomotion.

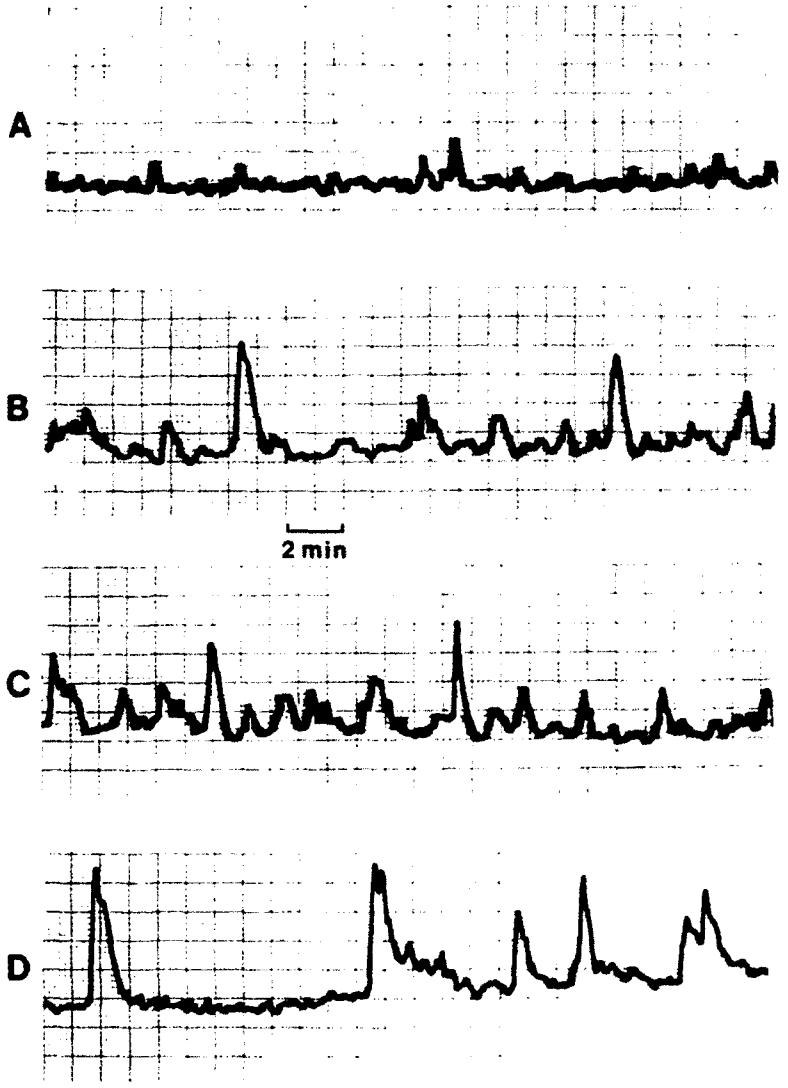

Figure 6. Microvascular vasoactivity, demonstrated by representative laser Doppler tracings of skeletal muscle blood flow. Note that spontaneous changes in flow are unpredictable, are neither regular or rhythmic, nor are these patterns necessarily repetitive. The flow patterns representative of vasoactivity are clearly distinct from those representing either inactivity or vasomotion.

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